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(54) Title: METHOD FOR THE TREATMENT OF MANIA AND BIPOLAR DISORDER

(57) Abstract

The present invention is a novel therapeutic use of pregabalin, its derivatives, and the pharmaceutical salts thereof. The compounds are useful in the treatment of mania in all its various forms whether acute or chronic, single or recurrent, and whether or not it is associated with depression. The invention further includes the preventive treatment of bipolar disorder.

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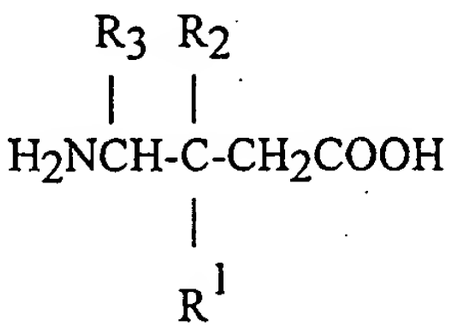
METHOD FOR THE TREATMENT OF MANIA AND BIPOLAR DISORDER

BACKGROUND OF THE INVENTION

United States Patent Number 5,563,175 and its family relate to compounds that are analogs of glutamic acid and gamma-aminobutyric acid (GABA).



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wherein R_1 is a straight or branched alkyl group having from 1 to 6 carbons, phenyl, or cycloalkyl having from 3 to 6 carbons, R_2 is hydrogen or methyl; and R_3 is hydrogen, methyl, or carboxyl. The compounds are useful in antiseizure therapy and for CNS disorders such as epilepsy, Huntington's Chorea, cerebral ischemia, Parkinsonism, tardive dyskinesia, and spasticity. The compounds are recited as also possibly useful as antidepressants, anxiolytics, and antipsychotics.

United States Patent Application Serial Number 09/043358 covers the compounds of Formula I above in the treatment of pain.

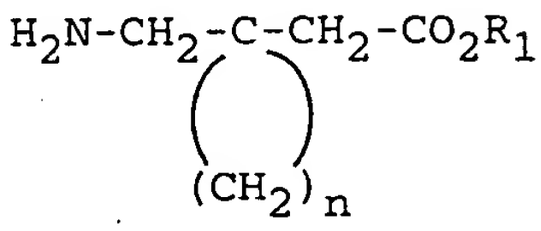
United States Patent Application Serial Number 60/050736 covers the compounds of Formula I above in the treatment of inflammation.

United States Patent Application Serial Numbers 60/056753 and 60/074794 cover the compounds of Formula I above in the prevention and treatment of gastrointestinal damage such as inflammatory bowel disorders (IBD) and inflammatory bowel disorder (IBD).

United States Patent Application Serial Number 60/072397 covers the compounds of Formula I above in the treatment of skeletal and muscular pain.

There is no disclosure in the above to make obvious the present invention of the uses of the compounds of Formula I in the treatment of mania and bipolar disorder.

United States Patent Numbers 4,024,175 and 4,087,544 teach cyclic amino acids of formula



wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6 and the pharmaceutically acceptable salts thereof.

The compounds disclosed in the above United States patents are useful for the therapy of certain cerebral diseases, for example, they can be used for the treatment of certain forms of epilepsy, faintness attacks, hypokinesia, and cranial traumas. Additionally, they bring about an improvement of cerebral functions and thus are useful in treating geriatric patients. Particularly valuable is 1-(aminomethyl)-cyclohexane-acetic acid (gabapentin).

United States Patent Number 5,084,479 teaches the compounds of the above formula for therapeutic use in neurodegenerative disorders such as Alzheimer's, Huntington's, Parkinson's, and Amyotrophic Lateral Sclerosis. It also teaches the use of the compounds in the treatment of acute brain injury such as stroke, head trauma, and asphyxia.

United States Patent Number 5,025,035 teaches the use of the compounds of the above formula for depression.

United States Patent Application Serial Number 08/281285 teaches the use of the compounds of the above formula to treat anxiety and/or panic disorders.

SUMMARY OF THE INVENTION

The present invention relates to novel therapeutic uses of a known compound, pregabalin, its derivatives, and pharmaceutically acceptable salts. Pregabalin is (S)-3-(aminomethyl)-5-methylhexanoic acid. The invention concerns a method for treating the symptoms of mania in a human in need of such treatment. This method includes, but is not limited to the treatment of mania in all its various forms whether acute or chronic, single or recurrent episode, and

associated with depression or not. The invention further includes the preventive treatment of bipolar disorder in persons predisposed to this disorder.

Episodes of acute mania are characterized by elevated or irritable mood, disturbed sleep, grandiosity, increased motor activity, pressured thinking, distractibility and poor concentration, impaired judgment, and sometimes psychotic symptoms. The irritability can lead to outbursts of angry or aggressive behavior. Often the episodes are preceded by a period of disturbed sleep. The distractibility makes the patient move endlessly from one activity to another often to the detriment of their physical, occupational, and social well-being. The impact of these behaviors is further aggravated by the lapses of judgment and poor decision-making that is characteristic of this illness.

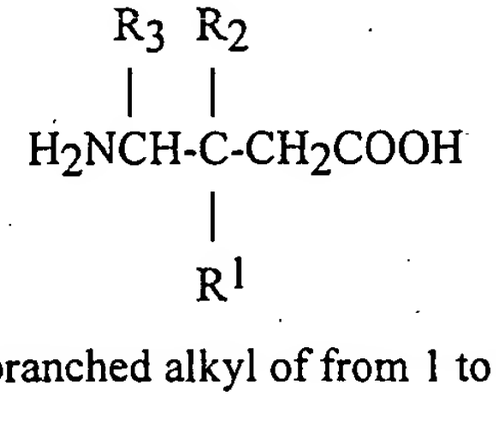
Episodes of mania occur in patients who suffer from bipolar disorder which is an illness characterized by alternating cycles of depression and mania. This disorder is distinct from the more common form of depression, called Major Depressive Disorder, in which patients only experience recurrent episodes of depression but no mania. Bipolar disorder can be diagnosed by the clinical evaluation of patients using the criteria specified in the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association. In this nomenclature system, bipolar disorder is subsumed under the broader class of Mood Disorders and is clearly distinguished from the Anxiety Disorders and from Organic Mental Disorders.

In studies of healthy subjects and patients suffering from anxiety, pregabalin has been noted to induce sedative and calming effects. These effects will be beneficial in the symptomatic treatment of patients suffering from mania who exhibit irritability, distractibility, and poor judgment. This is a novel use for pregabalin which would not be obvious to a medical practitioner of ordinary skill.

Pregabalin has also been found to enhance sleep. This effect will be beneficial in acute mania and will also lead to reducing the risk for onset of a new episode of mania in a predisposed individual. Thus, the prophylactic use of pregabalin for bipolar disorder is also taught.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel methods of treating mania and/or bipolar disorder in a mammal in need of such treatment. The treatment comprises administering in unit dosage form an effective amount of a compound of formula



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wherein R_1 is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or cycloalkyl of from 3 to 6 carbons; R_2 is hydrogen or methyl; and R_3 is hydrogen, methyl, or carbonyl.

The most preferred compound is (S)-3-(aminomethyl)-5-methylhexanoic acid.

Pharmaceutical compositions of the compound of the present invention or its salts are produced by formulating the active compound in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are

usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents.

The percentage of the active ingredients in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present.

Routes of administration of the subject compound or its salts are oral or parenteral. For example, a useful intravenous dose is between 5 and 50 mg and a useful oral dosage is between 20 and 200 mg. The dosage is within the dosing range used in epilepsy treatment or as would be with the needs of the patient as described by the physician.

A unit dosage form of the instant invention may also comprise other compounds useful in the therapy of neurodegenerative diseases.

The advantages of using the compounds of Formula I, especially pregabalin, in the instant invention include the relatively nontoxic nature of the compound, the ease of preparation, the fact that the compound is well-tolerated, and the ease of IV administration of the drug. Further, the drug is not metabolized in the body.

The subjects as used herein are mammals, including humans.

The usefulness of compounds of Formula I above and the salts thereof as agents for mania in all its various forms and in the preventative treatment of bipolar disorder is demonstrated in its effects on the mental functions of patients. These effects were observed during epilepsy clinical trial. See Table 1 below wherein the effects beneficial to healthy volunteers and anxious patients with bipolar disorder are presented.

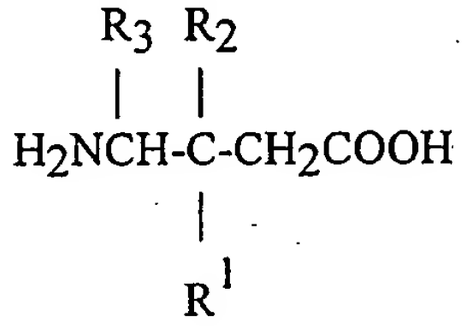
TABLE 1

Subject No.	Symptom(s)	Effect of Pregabalin
1	Anxiety, restlessness	Calming effect, sleepiness
2	Insomnia, fearfulness	Improved sleep
3	None	Relaxation, sense of well-being
4	None	Exhilaration, relaxed feeling
5	None	Drowsiness

CLAIMS

What is claimed is:

1. A method for treating the symptoms of mania in a mammal in need of said treatment which comprises administering a therapeutically effective amount of a compound of formula



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or a pharmaceutically acceptable salt thereof wherein R_1 is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or cycloalkyl of from 3 to 6 carbons; R_2 is hydrogen or methyl; and R_3 is hydrogen, methyl, or carbonyl.

2. A method according to Claim 1 wherein the compound administered is a compound of Formula I wherein R_3 and R_2 are hydrogen, and R_1 is $-(CH_2)_{0-2}$ -i C_4H_9 as an (R), (S), or (R, S) isomer.

3. A method according to Claim 1 wherein the compound administered is named (S)-3-(aminomethyl)-5-methylhexanoic acid or 3-aminomethyl-5-methylhexanoic acid.

4. A method according to Claim 1 wherein the mania is acute.

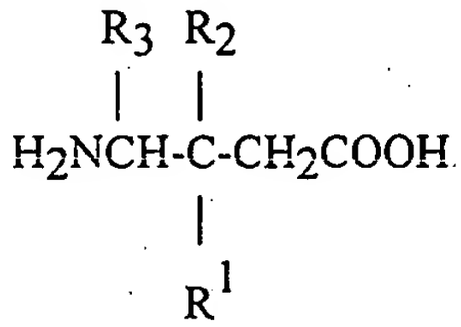
5. A method according to Claim 1 wherein the mania is chronic.

6. A method according to Claim 1 wherein the mania is a single episode.

7. A method according to Claim 1 wherein the mania is recurring.

8. A method according to Claim 1 wherein pregabalin is administered.

9. A method for treating and/or preventing bipolar disorder in a mammal in need of said treatment which comprises administering a therapeutically effective amount of a compound of formula



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or a pharmaceutically acceptable salt thereof wherein R_1 is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or cycloalkyl of from 3 to 6 carbons; R_2 is hydrogen or methyl; and R_3 is hydrogen, methyl, or carbonyl.

10. A method according to Claim 9 wherein the compound administered is pregabalin.

INTERNATIONAL SEARCH REPORT

Inte Jonal Application No
PCT/US 99/18981

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 23383 A (UNIV NORTHWESTERN) 25 November 1993 (1993-11-25) page 1, line 7-15 page 6, line 18-27 page 14, line 1-21; examples 1-3 ---	1-10
X	WO 98 17627 A (BRYANS JUSTIN STEPHEN ;HORWELL DAVID CHRISTOPHER (GB); KNEEN CLARE) 30 April 1998 (1998-04-30) page 25, line 7 -page 26, line 1; examples 1,2 page 29, line 1 -page 30, line 3; claims 1-7,12-14 ---	1,4-7,9
P,X	WO 99 08667 A (AKUNNE HYACINTH CHI ;HEFFNER THOMAS GARY (US); WARNER LAMBERT CO () 25 February 1999 (1999-02-25) page 1, line 17-22; claims 7-12,19-24 -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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1 February 2000	08/02/2000

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